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Liquid Biopsies in Breast Cancer: Revolutionizing Early Diagnosis and Disease Monitoring

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Abstract

Breast cancer remains a leading cause of morbidity and mortality among women worldwide, with early detection and timely disease monitoring critical for improving outcomes. Traditional tissue biopsies, though informative, are invasive and often limited in capturing tumor heterogeneity. Liquid biopsies have emerged as a minimally invasive alternative, offering real-time insights into tumor dynamics by analyzing circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), extracellular vesicles, and microRNAs in body fluids. These biomarkers enable early detection, prognostication, therapy response assessment, and monitoring of minimal residual disease, potentially guiding personalized treatment strategies. Despite challenges such as low biomarker abundance in early-stage disease and lack of standardized assays, liquid biopsies hold transformative potential in clinical oncology. This review highlights current technologies, clinical applications, limitations, and future perspectives, emphasizing their role in revolutionizing breast cancer diagnosis and disease management.

Keywords: Liquid biopsy, circulating tumor DNA, Circulating tumor cells, Breast cancer diagnosis, Disease monitoring

Introduction

Breast cancer is the most commonly diagnosed malignancy among women globally and remains a major cause of cancer-related mortality. Early detection is critical, as prognosis and survival outcomes are strongly influenced by the stage at diagnosis. Conventional diagnostic approaches, including tissue biopsy and imaging, provide valuable information on tumor histology and molecular characteristics. However, these methods are invasive, often limited to a single tumor site, and may fail to capture the spatial and temporal heterogeneity of tumors, which is crucial for guiding personalized therapy [1-2].Liquid biopsy has emerged as a minimally invasive, dynamic tool that enables the detection and monitoring of tumor-derived components in body

fluids, primarily blood. Key analytes include circulating tumor DNA (ctDNA), circulating tumor cells (CTCs), extracellular vesicles, and microRNAs, which collectively provide a comprehensive snapshot of tumor biology in real time. Unlike traditional biopsies, liquid biopsies offer the ability to monitor tumor evolution, assess therapy response, detect minimal residual disease, and identify emerging resistance mutations without repeated invasive procedures [3-4].This narrative review explores the current landscape of liquid biopsy technologies in breast cancer, emphasizing their role in early detection, disease monitoring, and clinical decision-making. The review also addresses existing challenges, limitations, and future directions, highlighting the potential of liquid biopsies to transform breast cancer management and improve patient outcomes.

Liquid Biopsies in Early Breast Cancer Detection

Early detection of breast cancer is pivotal in improving survival outcomes, yet conventional diagnostic approaches, such as mammography and tissue biopsy, have inherent limitations. Imaging modalities may be less sensitive in women with dense breast tissue, and tissue biopsies, while definitive, are invasive and often provide information from a single tumor region, missing the heterogeneity that characterizes many breast cancers [5-6].Liquid biopsies offer a minimally invasive alternative capable of detecting molecular signals of disease even before clinical or radiologic manifestations. Circulating tumor DNA (ctDNA), a fragment of DNA released into the bloodstream from apoptotic or necrotic tumor cells, can carry tumor-specific mutations, methylation patterns, and copy number alterations. Sensitive molecular assays can detect ctDNA at very low concentrations, providing a window into the presence of early-stage malignancy. Studies have shown that ctDNA can identify tumor-specific alterations in patients with localized breast cancer, highlighting its potential as an early diagnostic tool [7-10].

Circulating tumor cells (CTCs), intact cancer cells shed from the primary tumor into the bloodstream, also play a critical role in early detection. Even in early-stage breast cancer, low levels of CTCs can be detected, offering prognostic insight and the potential to anticipate disease recurrence. Additionally, exosomes and extracellular vesicles, which carry nucleic acids and proteins from tumor cells, provide another layer of information, reflecting tumor biology in real time [11-13].The integration of liquid biopsy with conventional imaging holds promise for improving diagnostic accuracy. For example, combining ctDNA analysis with mammography or MRI can enhance the sensitivity of screening, particularly in high-risk populations. Moreover, longitudinal sampling allows for continuous monitoring, enabling the detection of early molecular changes that may precede overt tumor development [14].

Role of Liquid Biopsies in Disease Monitoring and Prognostication

Beyond early detection, liquid biopsies have emerged as a powerful tool for monitoring disease progression and guiding prognostication in breast cancer. Traditional imaging and tissue biopsies provide static snapshots of the tumor, often failing to capture dynamic changes or the emergence of resistant clones during therapy. In contrast, liquid biopsies enable real-time assessment of tumor biology, offering critical insights into treatment response, minimal residual disease (MRD), and relapse risk [15-17].**Circulating tumor DNA (ctDNA)** is particularly valuable in this context. Quantitative changes in ctDNA levels often correlate with therapeutic response, frequently preceding radiologic evidence of tumor regression or progression. Persistent or rising ctDNA after surgery or systemic therapy can indicate residual disease or early recurrence, allowing clinicians to adjust treatment strategies proactively. Furthermore, ctDNA can reveal the emergence of resistance mutations, such as ESR1 mutations in hormone receptor-positive breast cancer, informing the selection of subsequent targeted therapies [18-19].

Circulating tumor cells (CTCs) provide complementary prognostic information. Elevated CTC counts during or after treatment are strongly

associated with poorer outcomes, including higher risks of recurrence and reduced overall survival. Molecular characterization of CTCs can also uncover actionable genetic alterations, helping to personalize therapy in metastatic or high-risk patients [20-21].**Exosomes and extracellular vesicles** serve as additional biomarkers for monitoring disease. By carrying proteins, RNA, and DNA reflective of tumor biology, these vesicles allow for longitudinal evaluation of tumor dynamics and may provide early indications of therapeutic resistance or metastatic potential [22].The integration of liquid biopsy into routine clinical monitoring has the potential to transform prognostication and treatment planning. Serial sampling enables a "real-time" view of tumor evolution, helping clinicians anticipate relapse, tailor therapy intensity, and optimize the timing of interventions. However, challenges remain, including the need for highly sensitive assays, standardization across laboratories, and robust clinical validation to ensure reproducibility and reliability of results [23].

Clinical Applications and Current Limitations

Liquid biopsies have rapidly emerged as a versatile tool in the clinical management of breast cancer, providing a minimally invasive window into tumor biology. Their capacity to capture tumor-derived biomarkers from blood or other body fluids allows clinicians to make more informed decisions across multiple stages of patient care.

Clinical Applications:

1. **Early Detection in High-Risk Populations:** Liquid biopsies can detect tumor-specific genetic and epigenetic alterations in asymptomatic individuals, particularly those with hereditary risk factors such as BRCA1/2 mutations. This capability offers the potential for earlier intervention, even before radiological evidence of disease.
2. **Monitoring Therapeutic Response:** Serial assessment of circulating tumor DNA (ctDNA) or circulating tumor cells (CTCs) can provide real-time feedback on treatment efficacy. Changes in biomarker levels often precede imaging-based assessments, enabling clinicians to adjust therapy proactively.
3. **Minimal Residual Disease (MRD) Assessment:** After surgical resection or adjuvant therapy, the presence of ctDNA can indicate residual disease, helping to identify patients at higher risk of relapse who may benefit from intensified monitoring or therapy.
4. **Detection of Acquired Resistance:** Liquid biopsy allows the identification of mutations or molecular alterations associated with therapeutic resistance. For example, emerging ESR1 mutations in hormone receptor-positive breast cancer can be detected, guiding timely modifications in treatment strategies.
5. **Precision Medicine and Companion Diagnostics:** Molecular profiling through liquid biopsies supports personalized therapy selection, tailoring treatment based on the evolving tumor landscape and improving clinical outcomes [24].

Current Limitations:

Despite their potential, several challenges limit the routine clinical use of liquid biopsies:

- **Low Biomarker Abundance in Early-Stage Disease:** Early tumors release minimal ctDNA or CTCs, making detection technically challenging and sometimes unreliable.
- **Lack of Standardization:** Variations in sample collection, processing, and assay methods across laboratories hinder reproducibility and broad clinical adoption.
- **Interpretive Complexity:** Tumor heterogeneity, transient biomarker fluctuations, and background mutations in cell-free DNA can complicate result interpretation.
- **Cost and Infrastructure:** High costs and the need for specialized laboratory equipment and expertise restrict widespread implementation, particularly in low-resource settings [24].

Conclusion

Liquid biopsies represent a transformative advancement in the management of breast cancer, offering a minimally invasive and dynamic

approach to diagnosis, disease monitoring, and prognostication. By analyzing circulating tumor DNA, circulating tumor cells, extracellular vesicles, and other tumor-derived biomarkers, liquid biopsies provide real-time insights into tumor biology, enabling earlier detection, assessment of therapeutic response, identification of minimal residual disease, and detection of emerging resistance mutations.While challenges such as assay sensitivity, standardization, and interpretation of results remain, ongoing technological innovations and clinical validation studies are steadily addressing these limitations. Integration of liquid biopsies with conventional imaging and tissue-based diagnostics holds promise for a more comprehensive, personalized approach to breast cancer care.

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